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AWARD NUMBER: DAMD17-02-1-0040

TITLE: Effects of Androgen Blockade on Cognitive Function and Quality of Life in Men with Prostate Cancer

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PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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14. ABSTRACT The purpose of this project was to examine the nature and severity of cognitive impairments experienced by men undergoing continuous androgen deprivation or intermittent androgen deprivation treatment (ADT). The cognitive abilities of androgen deprivation patients were compared with those of a sample of healthy men. We undertook collection of data from 40 men on intermittent or continuous ADT, and an age- and education-matched sample of 34 control subjects. Our major hypothesis was that patients undergoing ADT will experience impairments in those cognitive abilities reported in the research literature to be related to androgen levels (e.g., spatial ability, working memory for visual information). Bureaucratic requirements (largely related to institutional research board and General Clinical Research Center reviews) delayed the start of the project by nearly 20 months, necessitating two no-cost extensions. Data collection is complete, and the data have been entered into a database. Because analysis of the data is only now getting underway, there are as yet no results to report. We anticipate that data analysis will be completed during the fall of 2006, with at least one paper on the primary findings submitted for publication by the end of the calendar year.					
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FINAL REPORT FOR AWARD NUMBER DAMD17-02-1-0040
Cognitive Functioning Among Men with Stage IV Prostate Cancer Undergoing
Combined Androgen Deprivation (CAD) Therapy

Introduction

Hormonal treatment of prostate cancer by means of androgen deprivation treatment (ADT) can be an effective means of inducing tumor regression and delaying progression of the disease. The treatment, however, adversely affects quality of life (QOL), causing fatigue, depression, impotence, and loss of libido. Anecdotal evidence suggests that cognitive function also may be negatively affected. Because men with prostate cancer may survive for many years if the disease is suppressed, the identification of possible negative influences of life-prolonging treatment on their QOL, and the development of means to treat them, is of great importance. The research questions we are investigating address the relationship between sex steroid levels and different aspects of cognitive functioning. Our specific aims are to: 1) assess whether there is evidence of cognitive impairment among patients on ADT therapy; 2) assess the nature and severity of that impairment; 3) determine whether any cognitive deficits observed are related to testosterone (T) suppression, decreased estrogen level, or both; and 4) examine the relationship among performance on cognitive measures, steroid levels, and QOL. We have examined men on both continuous and intermittent ADT, and a matched sample of control subjects using tests of working memory, information processing speed, and spatial perception, as well as verbal learning, fluency, and reasoning. Each subject was tested at multiple time points. In addition to evaluating cognitive performance and QOL, we obtained blood levels of T, estradiol, estrone, sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), and albumin, as well as salivary cortisol levels at each time point.

Body of Report

This project faced numerous delays related to institutional approvals and issues with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). As noted in the original statement of work (Appendix A), we had anticipated that data collection would begin by the fourth study month. In fact, we only began subject recruitment in the final quarter of calendar year 2002. This delay was a result of requirements imposed by several layers of bureaucracy at the University of Colorado at Denver and Health Sciences Center (UCDHSC) related to human subjects research and to the use of the resources of the University's General Clinical Research Center (GCRC). A chronology of institutional review-related activities may be found in Appendix B, which contains the narrative portion of the Annual Report for the first project year.

The nearly 20-month delay in beginning subject recruitment necessitated a request for two no-cost extensions, the first of which ended in February 2006, and the second ending 6 August 2006. The requests for these extensions are included in Appendices C and D.

We initially planned to recruit patients from multiple sites participating in a Southwestern Oncology Group (SWOG) Continuous Androgen Deprivation (CAD) research protocol (e.g., Wayne State University, University of Arkansas). Because the GCRC, which funded the cost of all lab work for the study, declined to conduct assays on blood collected at other universities and because of the extraordinarily long delays we experienced in obtaining institutional approval just within our own institution, we were forced to discontinue plans to involve secondary data collection sites.

To ensure adequate enrollment, a new recruitment source was added to the study protocol. The investigators arranged to enroll prostate cancer patients being seen at Western Urologic Research Center (WURC), in Wheat Ridge, Colorado. This specialty private practice in the Denver area has a large patient population and a history of participation in clinical research. The involvement of WURC, in addition to our own patient population at UCDHSC, provided a sufficiently large pool of subjects that we were able to

complete data collection for ADT subjects ($n = 40$) and age- and education-matched controls ($n = 34$) in July 2006.

In the original proposal (see Appendix E), we proposed to collect data at three time points. Patients on intermittent ADT were to be administered cognitive tests: 1) at baseline (i.e., before beginning treatment or 12-16 weeks after discontinuation of androgen blockade); 2) 12-16 weeks following resumption of androgen blockade; and 3) 12-16 weeks after discontinuation of androgen blockade. Patients on continuous ADT also were to be examined at three time points: 1) at baseline (before ADT if possible or at least 12 weeks after discontinuing ADT; 2) after another 12-16 weeks of continuous ADT; and 3) after another 12-16 weeks of ADT. Control subjects also were to be administered the tests on three occasions: 1) at baseline; 2) after 12-16 weeks; and 3) after another 12-16 weeks. This design was based on the findings of Akakura et al. (1993), who reported that, on average, serum T returns to the normal range eight weeks following the discontinuation of androgen suppressing medications (range 1-26 weeks). By waiting three to four months after cessation of ADT, we expected that serum T levels would be within normal limits for most participants.

Experience during the course of this project suggested that T suppression may last far longer than previously reported. Our data show that many subjects remain suppressed at castrate levels even several months following an injection of androgen suppressing medications. In fact, recent research on androgen blockade, which was not available at the time the proposal was written, indicates that the time required for a return to normal levels of T is quite variable across subjects. Although some authors have found that a large percentage of subjects return to normal values within the time frame we anticipated (e.g., Morote et al., 2006; Mottet et al., 2005), others have reported rather lengthy periods of chemical castration. Kaku et al. (2006), for example, reported that the median duration of castrate T levels after ADT was six months, with a median time to normal T levels in the vicinity of 24 months. Longer time to recovery of normal T values was associated with increasing age, a characteristic of the men enrolled in the current study, and longer periods of therapy. The situation is further complicated by the fact that many older men have levels of serum T levels characteristic of hypogonadism (Harmon et al., 2001; T'Sjoen & Kauffman, 2006). This condition, in which T production is abnormally low, was found in some of the control subjects enrolled in our sample.

The long-lasting androgen suppression caused by ADT medications made it difficult to categorize men into the continuous ADT group versus the intermittent ADT group. Consequently, the investigators altered the study protocol, collapsing the intermittent and continuous ADT groups into a single ADT group, for whom we collected data when participants were suppressed and non-suppressed, as determined by assay results. This approach permits the comparison of ADT patients with controls, as well as the use of ADT subjects as their own controls, which was what we had planned to do from the outset. Documentation of this protocol amendment was submitted to the Department of Defense on December 13, 2004.

Key Research Accomplishments

We have completed data collection, and despite the end of the no-cost extension, are beginning data analysis. There are as yet no publications to report.

Reportable Outcomes

None to report. The bulk of data analysis should be completed by the end of October 2006, and we have begun writing a manuscript to report the primary findings regarding testosterone and cognition. We expect to submit between one and three manuscripts for publication by the end of this

calendar year. These will examine: 1) the relationships between sex steroids and specific aspects of cognitive functioning, 2) the relationships between sex steroids and quality of life; and 3) the effect of cortisol levels on cognitive functioning.

Conclusions

None to report as yet.

Project Staff

The following individuals played pivotal roles in the design, management, and conduct of the study: Jim Grigsby (Principal Investigator), Michael Glode, Angela Brega, Patricia DeVore, Jeff Bontrager, Marsha Paulich, Lane Bounds, Geri Fahrenbrink, Natasha Floersch, and Michelle Haarhues. Other individuals played limited roles on the project, performing specialized functions (e.g., IT support) as needs arose: Jim Beaudry, Sarah Braudrick, Tom Carlough, Jeff Loker, Karis May, Martha Powell, Dee Smyth, Chris Suess, and Karen Suess.

References

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APPENDIX A
STATEMENT OF WORK

Statement of Work

Task 1: Finalize study protocols and preparation for data collection (months 1-3).

- a. Prepare study brochure and consent form describing study for patients (month 1)
- b. Prepare written protocols for recruitment, data collection, and data management (months 1-2)
- c. Recruit and train data collectors (months 1-3)
- d. Prepare data collection instruments (months 1-2)
- e. Prepare database (months 1-3)

Task 2: Conduct of study (months 3-30).

- a. Begin subject recruitment and data collection (month 3)
- b. Begin first follow-up data collection [time point 2] (month 6)
- c. Subject recruitment completed (month 26)
- d. Time point 3 follow-up data collection completed (month 32)

Task 3: Interim data analysis (months 24-30).

- a. Preliminary data edits and transformations (months 24-27)
- b. Preliminary descriptive analyses (months 27-30)

Task 4: Annual reports.

- a. Prepare annual report for year 01 (months 11-12)
- b. Prepare annual report for year 02 (months 23-24)

Task 5: Final data analysis and report preparation (months 28-36).

- a. Specification of final data analyses (months 28-31)
- b. Conduct final data analyses (months 32-34)
- c. Write articles and submit for publication (months 28-36)
- d. Write final report (months 34-36)

APPENDIX B

ANNUAL REPORT FOR PROJECT YEAR ONE

ANNUAL REPORT FOR AWARD NUMBER DAMD17-02-1-0040

Cognitive Functioning Among Men with Stage IV Prostate Cancer Undergoing Combined Androgen Deprivation (CAD) Therapy

Introduction

Hormonal treatment of prostate cancer by means of androgen deprivation (AD) can be an effective means of inducing tumor regression and delaying progression of the disease. The treatment, however, adversely affects quality of life (QOL), causing fatigue, depression, impotence, and loss of libido. Anecdotal evidence suggests that cognitive function also may be negatively affected. Because men with prostate cancer may survive for many years if the disease is suppressed, the identification of possible negative influences of life-prolonging treatment on their QOL, and the development of means to treat them, is of great importance. The research questions we are investigating address the relationship between sex steroid levels and different aspects of cognitive functioning. Our specific aims are to: 1) assess whether there is evidence of cognitive impairment among patients on AD therapy; 2) assess the nature and severity of that impairment; 3) determine whether any cognitive deficits observed are related to T suppression, decreased estrogen level, or both; 4) evaluate the relationships between performance on specific cognitive tests and levels of certain sex steroids; and 5) examine the relationship among performance on cognitive measures, steroid levels, and QOL. We are examining men on continuous AD, a matched sample of men on intermittent AD, and a matched sample of healthy controls using tests of working memory, learning, verbal fluency, spatial perception, and verbal reasoning. Each subject is tested at three time points, approximately four months apart. We obtain T and estrogen levels, evaluate cognition, and assess QOL at each timepoint.

Body of Report

This project has been hampered by numerous delays related to institutional approvals and issues with the Health Insurance Privacy and Portability Act of 1996 (HIPAA). As noted in the original statement of work (Appendix A), we had anticipated that data collection would begin by the fourth study month. In fact, we only began subject recruitment in the final quarter of calendar year 2002. This delay was a result of requirements imposed by several layers of bureaucracy at the University of Colorado Health Sciences Center (UCHSC) related to human subjects research and to the use of the resources of the University's General Clinical Research Center (GCRC). A chronology of events follows.

We received a memorandum from the Adriene D. King, Ph.D, Human Subjects Protection Specialist with AMDEX Corporation, dated 17 December 2001 requesting minor revisions to the consent form and protocol (Appendix B, page 4). We submitted these revisions to the Colorado Multiple Institutional Review Board (COMIRB) from which we received approval on 11 February 2002 (Protocol Update and Protocol Amendment in Appendix C).

Assuming that we could begin recruitment expeditiously, we submitted a recruitment flyer to COMIRB and received approval from COMIRB on 4 February 2002. This flyer was subsequently distributed at an educational conference, held at the UCHSC, for men with prostate cancer. We received several calls in response from persons interested in serving as research participants, and they were added to a tracking database.

We had planned to use the resources of the GCRC in order to pay for a number of hormone assays. The University's GCRC is funded by the National Institutes of Health to support research studies, covering expenses that otherwise would need to be charged as direct costs to research grants. We learned that because the GCRC is located physically at University of Colorado Hospital, it was therefore necessary to seek the approval of the Hospital Research Resources Committee (HRRC) for the research. We submitted an application to the HRRC on 4 February 2002 (Appendix D), and it was tentatively approved on 27 February 2002, pending approval by the GCRC (Appendix E).

The GCRC meets monthly, and we submitted our application to the Center for review on 1 April 2002. In late April, we received a summary of the comments of the Scientific Advisory Committee (SAC) of the GCRC dated 4 April 2002 (Appendix F). The SAC had a large number of comments which needed to be addressed before approval would be given for the study. A serious illness and subsequent death in my family made it impossible to respond immediately, but on 30 August 2002 I submitted a detailed response to the SAC's critique of the project (Appendix G).

The SAC did not respond until 9 October 2002, at which time they continued to express reservations about the protocol and the assays we were requesting, although they had agreed with all the other points in my response of 30 August (Appendix H). On 14 October 2002, I responded to the SAC (Appendix I), and we received final approval from the GCRC on 31 October 2002 (Appendix J).

On 7 November 2002 we notified the HRRC that we had finally obtained GCRC approval to conduct the study (Appendix K). The HRRC then notified us that all study research personnel having contact with patients would have to go through the Hospital's credentialing process, including purified protein derivative (TB) testing. This was completed, and we received HRRC approval.

A required meeting of the investigators (Grigsby and Glodé) with GCRC clinical and administrative staff was scheduled for mid-December, at which time arrangements were made for use of the GCRC facilities, and lines of communication were established.

We once again began recruiting, and the use of a new flyer and an advertisement letter for eligible patients necessitated COMIRB approval once again. In addition, because the GCRC refused to pay for assays conducted using blood from patients not enrolled at the GCRC, we revised our plans for recruitment to include patients from Western Urologic Research Center, in Wheat Ridge, Colorado. This is a large specialty private practice in the Denver area which has the potential to refer a sizeable number of patients who can be enrolled at the GCRC. However, addition of this site as a source of patients required a protocol update approval by COMIRB. This was first submitted to COMIRB on 8 January 2003 (Appendix L), and they requested additional paperwork on 16 January (which we received on 21 January 2003, Appendix M). We are in the process of submitting an updated protocol amendment (Appendix N), and when approval has been obtained we will in turn submit notification to the Department of Defense IRB.

Finally, on 22 January 2003, we were notified that we must obtain the approval of the University of Colorado Hospital Cancer Center Protocol Review Committee, and we are in the process of preparing that application. Once final approvals are obtained, we already have a preliminary list of eligible subjects. Data collection is ready to begin, and we can start immediately.

Key Research Accomplishments

There are no substantive research accomplishments to report. We have dealt with various regulatory committees, a process that is now nearly complete. Arrangements have been made with the GCRC to begin data collection as soon as all necessary approvals have been obtained. Data collectors have been trained, and both a participant tracking database and a database for entry of participant data have been developed and debugged.

Reportable Outcomes

None to report.

Conclusions

None to report.

APPENDIX C
REQUEST FOR NO-COST EXTENTION
THROUGH FEBRUARY 2006



University of Colorado Health Sciences Center

Division of Health Care Policy and Research

Center for Health Services Research
13611 East Colfax Avenue, Suite 100
Aurora, CO 80011
Phone: 303-724-2400
Fax: 303-724-2530

November 9, 2004

Commander
U.S. Army Medical Research and Materiel Command
ATTN: MCMR-RMI-S
504 Scott Street
Fort Detrick, MD 21702-5012

Dear Sir or Madam:

We would like request a no-cost extension for the project entitled *Cognitive functioning among men with stage IV prostate cancer undergoing combined androgen deprivation (CAD) therapy*, DAMD17-02-1-0040. The project is behind schedule as a result of extensive delays in receiving institutional approval to conduct the study as well as difficulties identifying eligible cancer patients before they begin CAD therapy. (The lengthy process of obtaining institutional approval was described in the first and second annual reports.) Despite these delays, we are confident that the project can be brought to a successful conclusion. At this time, we are working with our clinical co-investigators to establish more effective procedures for screening and recruiting eligible patients. Further, the project team will soon begin recruitment of healthy control subjects. A 12-month no-cost extension through February 6, 2006 will allow the time needed to successfully complete the project, which has the potential to contribute significantly to our understanding of the effect of CAD therapy on the cognitive functioning and quality of life in men with prostate cancer.

Thank you for your consideration of this request. Please feel free to contact either of us if you have questions or need additional information.

Sincerely,

Jim Grigsby, PhD
Principal Investigator
(303) 724-2415

Angela G. Brega, PhD
Co-Investigator
(303) 724-2445

APPENDIX D
REQUEST FOR NO-COST EXTENTION
THROUGH AUGUST 2006



University of Colorado Health Sciences Center

Division of Health Care Policy and Research

Center for Health Services Research
13611 East Colfax Avenue, Suite 100
Aurora, CO 80011
Phone: 303-724-2400
Fax: 303-724-2530

December 14, 2005

Cheryl Lowery, Contract Specialist
U.S. Army Medical Research Acquisition Activity
820 Chandler Street
Fort Detrick, MD 21702-5014

Dear Ms. Lowery:

We are writing to request a 6-month no-cost extension for the project entitled *Cognitive functioning among men with stage IV prostate cancer undergoing combined androgen deprivation (CAD) therapy*, DAMD17-02-1-0040. As summarized below, and noted in the annual reports for years 1 and 2, the project is behind schedule as a result of extensive delays in receiving institutional approval. At this time, subject recruitment and testing is proceeding quickly and we are confident that a six-month extension through August 6, 2006 will allow for the successful completion of this important project.

Background

Androgen deprivation therapy can be an effective means of slowing tumor progression in prostate cancer patients. The treatment, however, adversely affects quality of life, causing fatigue, depression, impotence, and loss of libido. Anecdotal evidence suggests that cognitive functioning also may be negatively affected. Because men with prostate cancer may survive for many years if the disease is suppressed, the identification of negative side effects of life-prolonging therapy, and the development of means to treat them, is of great importance. The current study is designed to assess the presence, severity, and nature of cognitive impairment in men undergoing androgen deprivation therapy. We are examining a sample of men receiving androgen suppressing medications as well as a matched sample of control subjects using tests of working memory, learning, verbal fluency, spatial perception, and verbal reasoning. Each subject is tested at three time points, approximately two months apart. We obtain testosterone and estrogen levels, evaluate cognition, and assess quality of life at each time point.

Institutional Review Process

This project has been hampered by delays related to the need to obtain approval from five separate research review committees both within and outside the University of Colorado Health Sciences Center (UCHSC), not including that of the Department of Defense (DOD). As noted in the original statement of work, we had anticipated that data collection would begin by the third study month (March 2002). In fact, we were unable to begin subject recruitment until late 2002, with our first subject enrolled in early

2003. Subject recruitment then had to be halted for another nine months due to additional University regulatory requirements. In all, recruitment of study subjects was delayed for 18 months following the official start date of the project. The lengthy process of obtaining institutional approval is summarized below.

In accordance with DOD regulations, the study protocol and associated consent form were submitted to the UCHSC's institutional review board, known as the Colorado Multiple Institutional Review Board (COMIRB), prior to the finalization of the award. On July 26, 2001, initial approval for the project (which actually started January 7, 2002) was received. On December 17, 2001, we received a memorandum from Adriene D. King, Ph.D, Human Subjects Protection Specialist with AMDEX Corporation requesting minor revisions to the consent form and protocol. We submitted these revisions to COMIRB and subsequently received approval on February 11, 2002.

Because we planned to use the resources of the University's General Clinical Research Center (GCRC) to pay for the hormone assays conducted as part of the study, it was necessary to submit our research protocol for review by the GCRC's Scientific Advisory Committee (SAC), which we did on February 4, 2001. (The GCRC is funded by the National Institutes of Health to support research studies, covering expenses that otherwise would need to be charged as direct costs to research grants.) In late April, we received a summary of the comments of the SAC. The SAC had a large number of comments which needed to be addressed before approval would be given for the study. A serious illness and subsequent death in the Principal Investigator's family made it impossible to respond immediately, but on August 30, 2002, he submitted a detailed response to the SAC's critique of the project. The SAC responded on October 9, 2002, expressing continued reservations about the protocol and the assays requested. On October 14, 2002, additional documentation was submitted to the SAC. Final approval was received on October 31, 2002. A required meeting of the investigators with GCRC clinical and administrative staff was scheduled for mid-December, at which time arrangements were made for use of the GCRC facilities, and lines of communication were established.

Because the GCRC is located at the University of Colorado Hospital (UCH), it also was necessary to seek the approval of the UCH's Hospital Research Resources Committee (HRRC). We submitted an application to the HRRC on February 4, 2002, which was tentatively approved on February 27, 2002, pending approval by the GCRC. On November 7, 2002, we notified the HRRC that GCRC approval had been obtained, at which time the HRRC notified us that all study personnel having contact with patients would have to complete the Hospital's credentialing process, which includes TB testing; vaccination for varicella, rubella, rubeola, tetanus, Hepatitis A, and Hepatitis B; basic life support certification; and UCH employee orientation. The certification process was completed and HRRC approval finalized. At that time, subject enrollment began.

Subject enrollment was halted in January 2003, when we were informed that the UCH Cancer Center's Protocol Review and Monitoring Committee (PRMC) also would have to approve the study. This development was unexpected, as we originally had been informed that the Committee's approval was not necessary for non-therapeutic studies. The Committee's bimonthly meeting schedule and required several-week lead time for submitting an application resulted in a lengthy delay before approval was granted on July 2, 2003, 18 months after the project start date. At the time that PRMC approval was received, subject recruitment was reinstated. Recruitment letters were mailed to 116 members of the UCH's Prostate Cancer Support Group and 10 additional patients from co-investigator Dr. Glodé's oncology practice. Twenty-four individuals responded and screening/scheduling of study participants began.

Because the GCRC refused to pay for assays conducted using blood from patients not enrolled at the GCRC, we revised our plans for recruitment to eliminate all secondary data collection sites and to include Western Urologic Research Center (WURC), a large private practice in the Denver area, as an additional recruitment source for subjects who could be seen at the GCRC. An amended protocol was submitted to COMIRB on January 8, 2003 and was approved February 5, 2003.

The Health Insurance Portability and Accountability Act (HIPAA) Compliance Committee at WURC reviewed the study protocol as well. For more than two years, the Committee refused to allow the referral of WURC patients as possible study participants, out of concerns related to HIPAA regulations. Having greater experience with and knowledge of the privacy regulations included in HIPAA, the WURC HIPAA Committee ultimately decided in the Spring 2005 that collaboration as a recruitment source would in no way result in a violation of patient confidentiality. The approval of this final committee opened the door for the recruitment of large numbers of prostate cancer patients. Since June 2005, we have recruited 29 subjects and have access to a mailing list containing more than 500 names of men undergoing androgen deprivation therapy for the treatment of prostate cancer from which we send out regular mailings.

Although subject recruitment was delayed for 18 months, the project staff completed much important work during that time. As noted, review materials were prepared and submitted to five different research review boards as part of the initial review process. Further, protocol amendments have had to undergo the review and approval of COMIRB and GCRC, as well as the DOD's Human Subjects Protection group. During this time, recruitment flyers and letters were developed and received COMIRB approval. Informational presentations were conducted at local prostate cancer support group meetings and senior centers. Recruitment materials were posted in numerous medical clinics in the Denver metro area. All materials needed for the conduct of cognitive testing were purchased or developed. Data collectors completed certification and credentialing procedures required by the HRRC and were trained on the administration and scoring of the cognitive tests used as part of the study. An electronic database for storage of all patient tracking information and test data was designed, developed, and tested and procedures were developed for obtaining lab results from each of the four labs conducting assays for the study. In addition, HIPAA authorization forms were developed and underwent research review and approval after the implementation of the HIPAA privacy regulations.

Current Project Status

At this time, subject enrollment and testing is proceeding smoothly and quickly. Fifty-one subjects currently are enrolled in the study (34 prostate cancer patients undergoing androgen deprivation and 17 matched controls). Since June 2005, we have enrolled 38 subjects, have conducted 87 study visits, and are preparing another in a series of mailings to potential study participants under the care of doctors at WURC. Given that we have enrolled 10-15% of the WURC patients to whom recruitment letters have been sent to date, and that we have a mailing list of more than 500 WURC patients from which to recruit study subjects, we are confident that we will be able to complete enrollment in the next few months.

Project Extension Requested

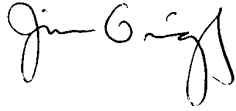
In November 2004, we requested and were granted a 12-month no-cost extension. This additional time has proven invaluable and has put us in a strong position to complete the project successfully. To ensure the successful completion of the project, we are requesting a six month extension of the project, which, if approved, would now end August 6, 2006. In addition to the 12-month extension we previously were granted, this additional six months will compensate for the 18 month delay in subject enrollment incurred at the beginning of the study in association with research review requirements.

August 11, 2006

Page 4

Thank you for your consideration of this request. Please feel free to contact either of us if you have questions or need additional information.

Sincerely,

A handwritten signature in black ink, appearing to read "Jim Grigsby". The signature is fluid and cursive, with the first name "Jim" and last name "Grigsby" clearly distinguishable.

Jim Grigsby, PhD
Principal Investigator
(303) 724-2415

A handwritten signature in black ink, appearing to read "Angela G. Brega". The signature is cursive and elegant, with the first name "Angela" and last name "Brega" clearly distinguishable.

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APPENDIX E

ORIGINAL PROJECT PROPOSAL

A. BACKGROUND

1. Introduction

We are submitting the proposed three-year study as a New Investigator Award Proposal, under the Department of Defense Congressionally Directed Medical Research Program (CDMRP) for prostate cancer. The proposed study, which is based on a sound rationale and a well-established body of literature regarding sex steroids and cognition, is relevant to the *Prostate Cancer Research Program* Fiscal Year 2001 Program Announcement insofar as the results would contribute to improvement in "the quality of life for individuals and their families living with prostate cancer" by addressing a previously neglected issue: the effects on cognition of hormone therapy for prostate cancer. We request funding for a period of 36 months.

Prostate cancer occurs chiefly in older men. It is an illness that can be cured or effectively managed in a large percentage of cases that are characterized by a relatively benign course. Even when the cancer has metastasized to distant sites, the likelihood of survival for five years or more, given proper management, can be good. Given that men with prostate cancer may require a number of years of therapy, factors influencing quality of life (QOL) are very important. Hormonal treatment of prostate cancer is widely used, and as discussed below, the suppression of endogenous sex steroids can have serious effects on physical, emotional, and cognitive well-being. The cognitive effects of hormone therapy have not previously been addressed. These effects and their implications for QOL are the focus of our study.

The proposal is a supplement to the National Cancer Institute (NCI)-funded study, *Phase III randomized study of intermittent versus constant combined androgen deprivation (Bicalutamide and Goserelin) in patients with stage IV prostate cancer responsive to such therapy*. That study carries the following protocol ID numbers: SWOG-9346, CAN-NCIC-JPR8, CLB-9594, INT-0162.

2. Prostate Cancer

When carcinoma has not spread beyond the prostate, the disease may be curable. If it has metastasized, especially to distant sites, the likelihood of mortality is high, although survival beyond five years is not unusual. A number of risk factors have been identified and survival is a function of such factors as heredity, localization of the tumor and presence of pelvic lymph node involvement, histologic grade (poorly differentiated tumors carry a worse prognosis), Gleason score, patient age, comorbidities, level of serum acid phosphatase and prostate specific antigen (PSA), diet, and DNA ploidy (Chodak et al., 1994; Gittes, 1991; Lieber, 1990; Matzkin et al., 1992; Nativ et al., 1989; Oesterling et al., 1987; Pisansky et al., 1993, 1997). The mean age of diagnosis is 72 years and the incidence of prostate cancer increases with advancing age. The primary treatment options for prostatic adenocarcinoma include surgery, radiation, and hormone therapy. Surgery (prostatectomy or cryosurgery) may be curative for men with low grade tumors, and without metastases, who are in good health (Shinohara et al., 1996; Zincke et al., 1994). Radiation therapy may be effective for patients with tumors of Grade I-III who are not candidates for surgery (Duncan et al., 1993). Both external beam radiation and interstitial implantation of radioisotopes are widely used (Ragde et al., 1997; Wallner et al., 1996). Radioisotope seeds are sometimes provided post-surgically when indicated by pathologic findings from the surgery.

3. Hormonal Treatment of Prostate Cancer

Prostate cancer tends to be androgen-dependent. That is, it grows rapidly in the presence of androgens (male hormones), but under conditions of androgen suppression, apoptosis is induced, and this leads to tumor regression. Hormonal therapy leads to reasonably good short-term management, but long-term outcomes often remain relatively unchanged as a result of androgen deprivation (AD). Over a period of time, tumors tend to become androgen-independent and growth begins to occur once again in spite of the androgen blockade. Depending on the grade and stage of tumor, as well as the age of the patient, hormone treatment may be used as an adjuvant approach. About 65% of men with distant metastases undergo hormonal therapy. Such therapies may take the form of surgical castration (orchiectomy) or the use of substances such as leuprolide or goserelin, which are luteinizing hormone releasing hormone (LHRH) agonists, and bicalutamide or flutamide, which are nonsteroidal anti-androgens. These agents block the production of testosterone (T), producing AD.

Androgen deprivation is a common approach to the treatment of Stage IV prostate cancer, sometimes using both anti-androgenic agents and LHRH agonists in what is referred to as combined androgen deprivation (CAD) therapy. However, there are two major drawbacks to AD. First, some data suggest that continuous therapy may lead to development of androgen-independent tumors. Second, the AD syndrome, which develops concomitant with this therapy, is associated with deleterious effects on QOL. For example, Herr and O'Sullivan (2000) reported that men on AD, compared with those not on AD, reported greater fatigue, greater emotional distress, and a lower QOL overall. Clark and associates (2001), in a study of 201 men treated with either chemical or surgical castration, found that among their subjects, 70% complained of hot flashes, 34% of nausea, and 81% of impotence. Other reported side effects include gynecomastia, breast tenderness, and loss of libido.

The adverse effects of continuous AD on QOL has led to the use of intermittent AD or intermittent CAD, as in the clinical trial protocol discussed above. In intermittent AD, following an induction phase of androgen blockade that reduces PSA to undetectable levels, AD therapy is discontinued. Patients then are observed until either their PSA rises or they show clinical signs of progressive disease. They then resume AD for a second round, after which time, if PSA is within normal limits, AD is again discontinued. The use of intermittent CAD as an alternative to continuous androgen suppression has been shown to improve QOL, reduce toxicity, facilitate recovery of libido and erectile functioning, and slow tumor progression toward an androgen-independent state by allowing some apoptotic recovery (Crook et al., 1999; Goldenberg et al., 1995, 1999; Higano et al., 1996; Wolff & Tunn, 2000). The NCI-funded Phase III trial, for which the proposed study is a supplement, was designed to provide data regarding the effectiveness of the continuous and intermittent approaches to CAD, with survival, PSA levels and changes, and several indices of QOL as endpoints. In this supplement, we expand the scope of QOL outcomes to include several specific aspects of cognitive functioning.

4. Sex Steroids and Cognition

In addition to findings of adverse effects reported in the literature, anecdotal reports by patients treated with continuous CAD at University of Colorado Hospital suggest that there may be a relatively high prevalence of cognitive impairment among this population. This has not previously been reported in the literature and is the focus of this proposed investigation. Our goal is to study whether it occurs, to determine the nature of such dysfunction, and to evaluate its relationship to hormonal status.

The mechanism(s) by which AD may interfere with cognitive functioning, as well as the nature of such impairment, are suggested by the scientific literature. Such effects could possibly be a result of the fatigue and dysphoric mood that often accompany AD, as either of these could disrupt the speed and capacity of information processing with consequent deleterious effects on sustained attention, learning, memory, and complex problem solving. It has been demonstrated, however, that certain sex steroids appear to have relatively direct effects on circumscribed aspects of cognition (for recent reviews see Erlanger et al., 1999; Henderson, 1997; Kimura, 1999; Sherwin, 1994a, b). Although the molecular means by which this is accomplished are not well understood, it appears that there are two primary mechanisms: 1) steroids influence the function of neurons by binding to intracellular receptors regulating gene expression; and 2) they function as neuromodulators, affecting the activity of ligand-gated channels and of specific classes of receptors coupled to G-proteins (Kelly & Wagner, 1999; Levin, 1999; Rupprecht & Holsboer, 1999; Wagner et al., 2001). Estrogen in particular appears to have neuromodulatory effects at cholinergic, noradrenergic, serotonergic, and GABAergic synapses.

Much of the research to date has focused on estrogen, on its general effects on cognition (e.g., Steffens et al., 1999, used the Mini Mental State Exam), and possible role as a neuroprotectant in Alzheimer's disease (Henderson, 1997; Honjo et al., 1989; Ohkura et al., 1994). A number of studies, however, have focused on specific aspects of cognition, with a particular emphasis on verbal fluency, fine motor tasks, and learning and memory. For example, it has been found that pre-menopausal women, acting as their own controls, show superior verbal fluency and fine motor functioning when estrogen levels are higher (as in the midluteal phase of their cycle) than when they are lower. Post-menopausal women taking estrogen and women who are hypoestrogenic from taking GnRH agonists but taking "add-back" estrogen (Sherwin & Tulandi, 1996),

compared with those not on estrogen, show similar results and experience beneficial effects on memory functioning (Baker et al., 2000; Hampson, 1990a, 1990b; Hampson & Kimura, 1988; Phillips & Sherwin, 1992; Sherwin, 1988, 1999). Even among healthy young men, higher levels of estradiol were associated with superior performance on measures of visual memory (Kampen & Sherwin, 1996). Such results have been obtained even among women with Alzheimer's disease (Asthana et al., 1999a, 1999b, 1999c). Not all findings have been positive, however. For example, Barrett-Connor and Goodman-Gruen (1999) reported no relationship between endogenous estrogen level and any measure of cognition among a sample of older women not on hormone replacement therapy (although they also reported a relationship between higher levels of T and two cognitive measures), but in that study the assays were conducted on blood drawn several years prior to the cognitive assessment. Overall, the findings have generally been consistent.

The effects of androgens on cognition have been less well characterized, although there is evidence that T is important for certain aspects of cognition. The strongest support comes for the role of T on tasks involving a strong spatial component, such as judging line orientation or mentally rotating visual images (Janowsky et al., 1994; Kimura, 1999; Van Goozen et al., 1995). Testosterone levels vary during the course of the day and across seasons, and moderate, but not low or high levels of T, are associated with better performance on tests of spatial ability (Kimura & Hampson, 1994; Moffat & Hampson, 1996). A recent report (Janowsky et al., 2000) suggested that working memory for visual material was improved by T supplementation among healthy older men, although working memory was unaffected among older women given estrogen supplements. An earlier study of 33 young men (with T levels in the normal range), however, found T levels unrelated to memory performance. There have been no studies reported in the literature such as the one we propose here.

Given that: 1) sex steroids influence the performance of a number of different kinds of cognitive tasks; 2) these effects appear to be mediated by neuromodulation and gene expression in the brain; and 3) androgen blockade must necessarily disrupt the influence of both androgens and estrogens at the neuronal level, there is a compelling need to investigate the relationships among AD, sex steroid levels, and performance on tasks that have been shown to be influenced by the plasma level of either estrogens or androgens. Importantly, cognitive impairment has frequently been shown to be associated with poorer QOL (e.g., Lloyd et al., 2000; Moore et al., 2000; Schrag et al., 2000). This may be the case especially among older adults, for whom cognitive impairment may be associated with impaired performance of activities of daily living (ADL), instrumental ADLs, and reduced independence (Grigsby et al., 1998; Kaye et al., 1990). The proposed research thus is poised to contribute significantly to an understanding of an important factor affecting QOL among men with prostate cancer and to better illuminate the influence of androgens on specific aspects of cognition.

5. Investigators

Given the nature of this research project, it is important that the research team bring multidisciplinary expertise to the project. The varied contributions of the key investigators are as follows:

Jim Grigsby, PhD, (P.I.) is a cognitive neuroscientist and health services researcher at the University of Colorado Health Sciences Center (UCHSC), where he is Associate Professor in the Department of Medicine (Geriatrics), and Senior Researcher at the Center for Health Services Research (CHSR). With 25 years of experience in cognitive neuropsychology as a researcher and clinician, his research has focused on specific cognitive functions (especially executive cognitive abilities, information processing, and working memory) in several different populations. He has extensive experience with neuropsychological measurement, has played a leading role in several national, multi-site studies, and is familiar with a wide range of data analytic techniques.

L. Michael Glodé, MD, is the Robert Rifkin Professor for Prostate Cancer Research in the Medicine Department at the University of Colorado Cancer Center. His laboratory continues an active research program on the effects of GnRH analogues on prostate cancer in various model systems. He has two full days of clinic each week, seeing approximately four new cases of prostate cancer, and follows >200 active patients at any one time. In addition, he speaks to local prostate patient advocacy groups such as UsToo and Man to Man throughout the Denver and front-range area. He will be responsible for recruiting patients from these resources and from the collaborating physicians locally and nationally.

Peter W. Shaughnessy, PhD, is Director of CHSR and Professor of Medicine (Division of Geriatrics) at UCHSC. He is a mathematical statistician with over 30 years experience in research methods in health care research focusing on chronic and degenerative conditions and diseases in elderly populations. He has served as a P.I. and lead statistician on over 25 national, multi-year studies involving primary data collection on patients in hospital, clinic, and long-term care settings. As a prostate cancer patient who has personally undergone and researched the primary therapies discussed in this proposal, he brings to bear on this research the perspectives of a health care researcher, a patient, and a statistical scientist.

Sanjay Asthana, MD, is a geriatrician, a staff physician at the GRECC at the VA Puget Sound Health Care System, and Research Associate Professor in the Department of Medicine at the University of Washington School of Medicine. Dr. Asthana's research interests have emphasized the clinical psychopharmacology and neuroendocrinology of gonadal steroids and cholinergic drugs in Alzheimer's disease and healthy aging. He will serve as a consultant regarding psychoneuroendocrinology and will help in data analysis and reporting.

Angela G. Brega, PhD, is a Research Associate in the School of Medicine at UCHSC and Research Associate at CHSR. Dr. Brega holds a PhD in psychology and is experienced in all phases of research design; instrument development; data collection, management, and analysis; and project management. She will contribute to all aspects of this study and, in particular, will serve as Project Manager, with oversight for data collector training, data collection, and statistical analysis.

B. HYPOTHESES/RATIONALE/PURPOSE

1. Rationale

The major purpose of this study is to add significant new knowledge to the field of prostate cancer research and improve the QOL for men with this illness. We will examine cognitive functioning to elucidate the presence, nature, and severity of cognitive deficits among men undergoing AD therapy and to assess and quantify the relationship of any such deficits to plasma levels of sex steroids. Our hypotheses and specific aims are based on the premise that androgen blockade interferes with neuromodulatory processes and gene regulation that influence performance on specific cognitive tasks.

2. Hypotheses

The hypotheses associated with this major purpose are as follows:

- a. Androgen deprivation therapy has a negative effect on cognitive functioning in men with prostate cancer. More specifically, this will be examined by testing the following two subhypotheses:
 - 1) Performance on selected measures of cognition will be worse for prostate cancer patients on AD than for subjects not on AD who have normal levels of T (this includes controls and off-treatment intermittent AD patients), after controlling for fatigue and depression.
 - 2) Patients on both continuous and intermittent, on-treatment, AD protocols will perform worse on cognitive measures than will age-matched healthy controls, after controlling for fatigue and depression.
- b. Performance on working memory and visual-spatial tests will be associated with plasma T level.
- c. Performance on verbal fluency and verbal learning and memory tests will be associated with plasma estradiol level.
- d. Performance on tests previously not shown to be affected by sex steroid levels (e.g., verbal reasoning) will remain unaffected by AD.
- e. Poor performance on measures of cognitive functioning will be correlated with poor QOL as measured by the SF-36.

Hypothesis *a* is the primary study hypothesis. To the extent that it is validated through empirical testing, the results of testing the remaining four hypotheses (*b* through *e*) will reveal further how and why the relationship in hypothesis *a* is effectuated.

C. OBJECTIVES

Specific Aims

To accomplish the overall goal described above and to guide us in testing our hypotheses, we propose the following specific aims. We intend to:

- assess whether there is evidence of cognitive impairment among patients on AD therapy;
- assess the nature and severity of that impairment, evaluating different aspects of cognition;
- use cognitive tests sensitive to fluctuations in levels of T or estrogen, and others that are unaffected by plasma sex steroid level, to evaluate whether the deficits observed are related directly to changes in the level of T, the level of estradiol, or of both;
- obtain plasma levels of T and estradiol at each data collection time point in order to evaluate the relationships between performance on specific cognitive tests and levels of these sex steroids; and
- examine the relationship between performance on cognitive measures and QOL.

D. METHODS

1. Overview

The research we propose will involve a prospective cohort study of prostate cancer patients receiving either continuous or intermittent CAD therapy. They will be compared with each other, and with a matched group of healthy control subjects, at each of three time points. In addition, within-subject performance of intermittent AD patients will be analyzed, using patients as their own controls, to determine whether AD is responsible for observed cognitive deficits. Each subject will be examined using a battery of cognitive tests and will be asked to give a blood sample on each occasion for measurement of T and estradiol levels.

This study will be conducted as a supplement to SWOG protocol 9346, which was discussed in the introduction to this application. In that study, following an initial induction phase involving eight courses (seven months) of CAD therapy, stage IV prostate cancer patients are randomized to one of two arms. Patients assigned to the first arm receive continuous CAD, even in the absence of disease progression (as determined by level of PSA). Individuals assigned to the second arm, following the induction phase, discontinue CAD therapy and are observed until either their PSA rises to approximately 20 ng/mL or they show clinical signs of disease activity. At that time, patients resume CAD for a second round of eight courses (seven months), after which time, if PSA is within normal limits, CAD is again discontinued. We propose to use patients already participating in both the intermittent and continuous arms of this SWOG protocol.

2. Recruiting

Subjects will be males aged 50 and older who meet the inclusion and exclusion criteria for the clinical trial. There will be two sources of participants with prostate cancer. First, CAD subjects will be recruited from centers participating in SWOG protocol 9346. We will recruit as many as possible from the University of Colorado Hospital, but will have access to patients being treated in other centers as well. Second, some participants will be enrolled who are not on the experimental protocol, but who are being treated by Dr. Glodé, who meet the inclusion and exclusion criteria and who are on intermittent or continuous AD. Healthy controls, matched on age (within five years) and education (within two years), will be recruited from the community. To minimize genetic and socioeconomic variance, we will first attempt to recruit brothers of patients who participate in the study. Control subjects also may be recruited from among the brothers of prostate cancer patients who participate in local support groups but who do not participate in the study. We have close contacts with several such groups. On the basis of power calculations (discussed below), we have determined that we will need approximately 22 subjects per group for mean comparisons with $\alpha = 0.05$, and 31 subjects per group if $\alpha = 0.01$. To deal with the likelihood of attrition due to mortality, exacerbation of prostate cancer, exacerbation of other chronic illnesses, development of new acute illnesses, and other factors that might affect this predominantly older sample, we plan to recruit 35 subjects per group.

3. Inclusion and Exclusion Criteria

All participants will be men aged 50 and older, fluent English speakers, and willing to provide informed consent for participation. They will conform to the inclusion and exclusion criteria for the CAD clinical trial. As these are quite detailed, they will only be summarized here.

- Adenocarcinoma of the prostate, with or without metastases to bone, brain, liver, or lung;
- Elevated PSA (5 ng/mL or greater);
- No concurrent biological response modifier therapy or chemotherapy; no concurrent hormonal therapy; and at least one year since any prior neoadjuvant or adjuvant hormonal therapy, or any prior finasteride;
- No concurrent radiotherapy other than palliation of painful bone metastases;
- No prior bilateral orchiectomy;
- No active medical illness precluding treatment or limiting survival;
- No second malignancy within five years except adequately treated nonmelanomatous skin cancer, in situ bladder cancer or other superficial cancer; and
- No history of neurologic disorder, head trauma with loss of consciousness, learning disability, mental retardation, history of alcoholism, or psychosis.

Controls will be healthy men aged 50 and above with no history of cancer chemotherapy, neurologic disorder, head trauma, learning disability, mental retardation, alcoholism, or psychosis. Because only adult men are affected, women and children are excluded. English-speaking minorities will be included in proportion to their representation in the clinical trial. The sample size is too small to permit meaningful ethnic comparisons.

4. Participating Sites

The primary data collection site will be the University of Colorado Hospital in Denver. Other sites participating in the Phase III trial may be used as well. The three most active SWOG, NCI, and ECOG sites have already enrolled a total of 253 patients, suggesting that we will have adequate numbers.

5. Consent Procedure

Consent will be obtained by an investigator thoroughly familiar with the clinical trial protocol. Consent will be sought in the clinic during a routine clinic appointment and the patient (or control) will be given time to consider the research and whether he wishes to participate. After receiving information on the study, he will be given an opportunity to ask any questions and inquiries will be made to determine whether he fully understands the requirements of participation and his rights as a subject. After signing an informed consent form, the subject will be given a copy of the consent and his consent will be documented in his clinic chart.

6. Data Collection Time Points

We will obtain baseline data on as many patients as possible. Since this is a supplement to a clinical trial, however, we may not have access to all patients before they have begun AD. However, the scientific literature on cognition and androgen levels strongly supports the assumption that adequate variation in androgen levels will occur for the intermittent AD group between on- and off-treatment periods. Comparing androgen levels and cognitive functioning scores of the intermittent AD group during the off-treatment period with the same variables for controls will provide an indication of whether AD may have a lasting effect on cognition beyond the period of blockade. In addition, because we will have blood hormone levels at each time point for each subject, we will be able to ensure the equivalence of the hormonal milieu, which is fundamental to our comparisons. Should there be variability across groups in this regard, we will use the actual levels, as well as number of on-treatment periods undergone and duration of those periods as covariates.

Patients on intermittent CAD will be administered cognitive tests: 1) at baseline (before beginning AD) if possible, or 12-16 weeks after discontinuation of androgen blockade; 2) 12-16 weeks following resumption of androgen blockade; and 3) 12-16 weeks after discontinuation of androgen blockade. Patients on continuous CAD also will be examined at three time points: 1) at baseline (before AD) if possible or after at least 12 weeks on AD; 2) after another 12-16 weeks of continuous AD; and 3) after another 12-16 weeks of AD. This design will allow comparison of the effect of CAD on cognition while controlling for practice effects. Control subjects also will be administered the tests on three occasions: 1) at baseline; 2) after 12-16 weeks; and 3) after another

12-16 weeks. According to Akakura et al. (1993), serum T returns to the normal range within a median of about eight weeks (range 1-26 weeks) of stopping suppression, so that by waiting for three to four months after cessation of CAD, we can be fairly certain that serum T levels will be within normal limits for most participants even without assays. Nevertheless, we will obtain T and estradiol assays at each time point. Because it will not be possible to obtain any off-treatment data for some continuous CAD patients, the crucial repeated measures comparisons for them versus the other two groups will be at time points 2 and 3.

Examination at each of the three time points will require about 90 minutes. To minimize fatigue, there will be a break midway through administration and more frequently if needed. For those unable to complete the testing in one sitting, they will be tested over two sessions. Data collectors will be trained to evaluate fatigue and asked to reschedule testing if fatigue appears to affect performance. To prevent unanticipated order effects in the cognitive assessment, the order of administration of tests will be randomized across subjects. To minimize circadian variability in performance (Blake, 1967), subjects will be scheduled for assessment at the time of day they prefer and these assignments will remain constant for each subject across time points.

7. Cognitive and Neuropsychologic Instruments

Following are the measures to be administered in this study, accompanied by brief discussion of their properties. Performance on certain of these has been shown to be dependent on level of T, of estrogen, or neither. Because T is converted into estradiol via aromatization, it is possible that cognitive effects observed as a result of T suppression could be a result of low levels of either of these hormones.

a. Working Memory

Working memory (Baddeley, 1990; short-term storage of information upon which cognitive operations simultaneously must be performed, or which is needed for performance of concurrent tasks) is often impaired among older adults (Raz, 2000). Among older men, working memory has been shown to be sensitive to T level (Janowsky et al., 2000). The following will be used as measures of working memory and immediate recall.

Letter Number Sequencing: A subtest of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; Wechsler, 1997) in which subjects are presented with mixed sequences of letters and numbers (e.g., 3-e-7-9-p), then must separate letters and numbers and repeat them in the proper sequence (e.g., 3-7-9-e-p). The test is a reliable and valid measure of verbal auditory working memory (Wechsler, 1997).

Visual Working Memory: This test involves recall of a set of abstract drawings presented in groups of 6, 8, 10, or 12, in different spatial arrangements on separate cards. Shown each card one at a time, the subject must touch a picture not previously touched in a series. An error occurs when the subject touches a card previously touched in that set (Petrides & Milner, 1982). This test was previously used by Janowsky and associates (2000) in their study showing that T affected working memory.

b. Speed and Capacity of Information Processing

Performance on most tasks is influenced by one's speed and capacity for processing information. Although these abilities have not typically been found to be associated with sex steroid levels (but see Asthana, 1999c), they are sensitive to depression and fatigue. The following are considered direct measures of these abilities.

Symbol Digit Modalities Test (SDMT): This is a measure of processing speed (Smith, 1968). Similar to the Digit Symbol subtest of the WAIS-III, the subject is required to provide the number associated with each of nine different symbols. Scores are based on the number of correct responses in a 90-second trial. Reliability is very good. Performance on the SDMT has been shown to be associated with a number of neurologic conditions, and with the P3 component of evoked potentials (Spreen & Strauss, 1998).

Grammatical Reasoning: An experimental measure of simple reasoning sensitive to deficits in speed and capacity of information processing (Baddeley, 1968), it consists of 32 simple declarative statements having systematic variations in grammatical construction (e.g., "A is followed by B," "B is not preceded by A"). Each is followed by the letters **AB** or **BA**. The subject must say whether each statement about the letters is true or false. The subject's score is the number of items answered correctly in three minutes.

c. Declarative Verbal Learning and Memory

Among women and men, verbal learning and memory have been found to be sensitive to estrogen level. The influence of estrogen in men is less clear than in women, but performance on the following tests might well be influenced by absence of estradiol. It might also be influenced by deficits in working memory.

Logical Memory Subtest of the Wechsler Memory Scale-III (WMS-III): A test of declarative verbal memory, involving immediate and 30-minute delayed recall for two short paragraphs read to the subject by the examiner (Wechsler, 1997). Interrater and test-retest reliabilities are > 0.90 (Wechsler, 1997). We will use only one of the two paragraphs at each time point. For repeat testing, we will use the second paragraph and equivalent paragraphs from the second edition of the WMS (Wechsler Memory Scale-Revised).

Rey Auditory Verbal Learning Test (RAVLT): A brief, easily administered auditory verbal learning test comprised of 15 unrelated concrete nouns repeated for five trials. Recall is requested after each presentation of the words. After the fifth trial, a second interference list is read to the subject, and after a 20-minute delay, both recall and recognition are tested for the first list. The scores of interest are the number of words correctly recalled after the first presentation, the number recalled by the fifth trial, the number of words recalled after 20 minutes, and 20-minute recognition. Different, parallel forms of the test are available for retesting.

d. Verbal Reasoning

Verbal reasoning has not been shown to be affected by sex steroid levels. It may serve as an important covariate in analyzing data from other cognitive tests. These tests will be administered to provide an estimate of verbal intellectual level and to determine whether performance on them is influenced by T level.

Similarities and Vocabulary Subtests of the WAIS-III: The Similarities and Vocabulary subtests (Wechsler, 1997) will be used to assess general verbal reasoning ability. These are relatively independent of memory and are highly correlated with the Wechsler verbal IQ score. We anticipate little change in either score and intend to use these subtests primarily to control for verbal intelligence.

e. Verbal Fluency

Tests of verbal fluency have been shown to be sensitive to estrogen level in women. Whether, and to what extent, they are affected by sex steroids in men is unknown.

Controlled Oral Word Association Test (COWAT): Commonly described as a test of verbal fluency or cognitive flexibility, the COWAT reflects the ability to generate information actively and is correlated strongly with measures of executive functioning. Over three trials, the subject must say as many words as he can think of in a 60-second period, starting with a given letter (F, A, and S). Reliabilities are very good to excellent (ranging from 0.70 to nearly 1.0; desRosiers & Kavanagh, 1987; Spreen & Benton, 1977).

f. Spatial Perception

Performance on tests of spatial perception has been found to be associated with T level. Among men, even relatively subtle variations in the level of this sex steroid may affect performance either positively or negatively. We will use the following tests.

Vandenberg and Kuse Mental Rotation Test: This consists of a number of line drawings of three-dimensional geometric objects (Vandenberg & Kuse, 1978). A stimulus figure is compared with four variations on this figure, one of which is identical to the stimulus figure except that it is drawn so it is rotated. The subject must select the identical rotated figure. This is the most commonly used test of mental rotation.

Benton Line Orientation Test: Two lines at different angles relative to the horizontal are presented on a card and the subject's task is to identify, on a second card, which of 12 different lines' angles match these. This test is a valid and reliable measure (Benton et al., 1983).

g. Depression

Depression and fatigue may affect performance on a number of the tests discussed above entirely independently of the influence of sex steroids or other factors. We, therefore, will collect data on these variables as covariates in the analysis. Depression will be evaluated using the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). This scale contains fewer items that might reflect physical disability than do other depression scales and has been demonstrated to be a reliable and valid measure of depression.

h. Quality of Life and Fatigue

Quality of life will be assessed using the SF-36, a general health status instrument used in the RAND Medical Outcomes Study (Ware & Sherbourne, 1992). The scale is reliable and valid as a measure of QOL (e.g., Andresen & Meyers, 2000; Lloyd et al., 2000). Scores on the fatigue subscale will be used to control for the effects of fatigue on performance. Subjects also will be asked to rate level of fatigue at each time point on a 10-point analog scale, noting current fatigue and average for the past week.

8. Hormone Assays

Blood will be drawn each time a patient is examined in order to conduct assays for T and estradiol (both free and bound). Samples will be analyzed at the UCHSC General Clinical Research Center. This will permit us to ensure the equivalency of subjects' hormonal milieu and to adjust statistically for differences if there is variability in sex steroid level in suppressed or non-suppressed states.

9. Training and Quality Control of Data Collectors

Data collectors at each center will be responsible for enrolling subjects and administering all instruments. Data collectors will be trained face-to-face by either Dr. Brega or Dr. Grigsby in the administration of each test. Data collectors will then administer complete sets of the tests on three occasions to persons who are not study participants. At least two of these administrations will be observed directly, videotaped, or observed via videoconference. Differences or problems in administration and scoring will be discussed and reconciled between observers and data collectors. For each data collector, the first three actual assessments of participants will be observed by video as well, and feedback given to the data collectors. After each data collector has completed 10-12 patient exams, she or he will again be observed by the investigators. We will conduct an interrater reliability analysis using 15 videotaped assessments of participants. Dr. Brega will be responsible for ensuring the accuracy of scoring. After a data collector has completed a total of 10-15 patient assessments, she or he will be observed again by the investigators.

10. Data Analysis

All data management and analysis will be conducted at CHSR under the supervision of Drs. Brega and Grigsby. Data will be double-entered to ensure quality control, with discrepancies resolved by review of original data forms. We will use SPSS and SAS for analysis.

To evaluate data integrity and completeness and to characterize the samples within each group, frequency distributions and descriptive statistics will be obtained. We then will assess mean differences among the groups on clinical and demographic factors. The overall analytic plan will include modeling cognitive functioning, using both mean differences (between continuous variables) and percent of persons classified as impaired (for dichotomous variables). Comparisons will be made over time and across the three patient cohorts included in this study. For continuous measures of cognition, repeated measures analysis of covariance (ANCOVA) and multivariate analysis of covariance (MANCOVA) will be used. An advantage of MANCOVA with the cognitive tests is that it limits the number of mean comparisons, hence avoiding inflation in experiment-wise Type I error rate. For example, MANCOVA might be used to examine working memory, with each test score as a dependent variable, treatment group as a fixed independent variable indicating on- or off-treatment status, and fatigue, depression, and T level as covariates. When multiple comparisons are made, we will use the Holm method (as opposed to those of Bonferroni or Dunn) of correction (Aickin & Gensler, 1996; Holm, 1979). For dichotomous measures, logistic regression models will be applied. We also will use multiple regression to assess the contribution of a number of different variables to specific dependent variables. Such variables as age, education, depression, comorbidity, verbal reasoning, and hormonal status may be included as covariates. In addition to these analyses, there are opportunities to profile patients at greatest risk of cognitive impairment (on variables such as age, education, comorbidity) using the approaches described above.

11. Statistical Power and Sample Size Estimates

The projected sample size of 35 patients per group was determined by estimating statistical power, then adding to the total in order to deal with possible problems resulting from attrition. We anticipate adequate power to detect small-to-moderate differences over time, as well as among the three groups. We estimated

necessary sample sizes to obtain power using repeated measures analysis of variance (ANOVA) with three conditions and a total of three measures per subject. Based on cognitive research in other contexts, we assumed an effect size of 0.4, which is about midway between what Cohen (1973) considered small (0.25) and medium (0.5) effect sizes. With this effect size, at $\alpha = 0.05$, 22 subjects are required to achieve power $(1-\beta) = 0.80$. At $\alpha = 0.01$, it would require 31 subjects to achieve $1-\beta = 0.80$.

12. Limitations of the Study

This proposed study has certain limitations, which we have addressed in the following ways. First, because of its dependence on subjects obtained primarily from a SWOG protocol, recruitment of an adequate local sample could be slow. We, therefore, will recruit patients from sites other than the University of Colorado Hospital. Second, because this is an ancillary study associated with a clinical trial, the clinical needs of patients always take precedence and it may, at times, not be possible to examine participants at a scheduled second or third visit. Intermittent CAD patients, for example, may need to resume androgen blockade in response to changes in their clinical condition. This is one of the reasons for sampling more patients than power calculations suggest are necessary. Third, despite the use of hormone assays and the use of tests sensitive to changes in the level of specific sex steroids, it may be difficult to draw conclusions about the unique effects of either T or estrogen on specific aspects of cognition. We may only be able to analyze correlations between test performance and sex steroid levels and perhaps draw inferences about the effect of the androgen blockade itself. Fourth, because of the limited sampling frame, we will need to enroll an unknown number of subjects who are already on an AD protocol and, therefore, will be unable to obtain pre-therapy baseline measures on some of the prostate cancer patients. However, the scientific literature on cognition and androgen levels strongly supports the assumption that adequate variation in androgen levels (and cognitive functioning, to the extent that our primary hypothesis is correct) will occur for the intermittent AD group between on- and off-treatment periods. Comparing the androgen levels and cognitive functioning scores of the intermittent AD group during the off-treatment period with the same variables for the control group will provide an initial indication of whether AD may have a lasting effect on cognitive functioning beyond the period of its direct administration. In addition, because we will have blood hormone levels at each time point for each subject, we will be able to ensure the equivalence of the hormonal milieu. Should there be variability across groups in this regard, we will be able to use the actual levels, as well as number of on-treatment periods undergone, and duration of those periods, as covariates.

13. Summary

The research we propose is highly responsive to the research priorities of the Department of Defense CDMRP Prostate Cancer Research Program. In particular, the proposed study, which is based on a sound rationale and a well-established body of literature on sex steroids and cognition--would contribute to improvement in "the quality of life for individuals and their families living with prostate cancer" by addressing a previously neglected issue: the effects on cognition of hormone therapy for prostate cancer. This represents innovative research on an important side effect of hormone therapy, regarding which there are no previous data. Hence, the New Investigator Award is an ideal vehicle for such a study. The Principal Investigator is experienced in the assessment of cognitive deficits in a number of populations--especially older adults, who will be the primary target of this study--and has some experience with the cognitive effects of breast cancer treatment, but has not conducted research in the field of prostate cancer. The research team is staffed with personnel highly skilled in medical oncology, sex steroid research, neurocognitive assessment, and the conduct of large-scale research projects. In short, this is a new and undeveloped, yet very important area of investigation that would benefit greatly from this proposed study.